Comparison of Propranolol and Hydrochlorothiazide for the Initial Treatment of Hypertension

I. Results of Short-term Titration With Emphasis on Racial Differences in Response

Veterans Administration Cooperative Study Group on Antihypertensive Agents

• **We compared hydrochlorothiazide and propranolol hydrochloride for monotherapy of hypertension by a double-blind study of 683 men who were titrated to less than 90 mm Hg diastolic BP or to 640 mg of propranolol or 200 mg of hydrochlorothiazide. Propranolol reduced systolic BP from 146.0±14.4 (SD) to 134.8±16.3 mm Hg and diastolic BP from 101.6±4.6 to 90.5±7.6 mm Hg. Hydrochlorothiazide lowered both systolic BP more effectively from 146.5±15.8 to 128.8±12.2 mm Hg and diastolic BP from 101.3±4.5 to 89.4±6.5 mm Hg. In blacks, hydrochlorothiazide lowered systolic BP 20.3±14.3 mm Hg *v* 8.2±12.2 mm Hg for propranolol; hydrochlorothiazide reduced diastolic BP 13.0±7.0 mm Hg *v* 9.5±7.0 for propranolol. In whites, the systolic BP reductions were 15.3±12.0 mm Hg for hydrochlorothiazide *v* 13.2±13.1 mm Hg for propranolol; diastolic BPs were 10.9±5.7 mm Hg for hydrochlorothiazide and 12.6±6.6 mm Hg for propranolol. In blacks treated with hydrochlorothiazide, 71.3% achieved diastolic BP of less than 90 mm Hg, *v* 53.5% with propranolol. There was no racial difference in dose response to propranolol, but blacks required much less hydrochlorothiazide to achieve control. We conclude that in this short-term study propranolol was as efficacious as hydrochlorothiazide in whites, but the latter was more effective than propranolol in blacks.**

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ALTHOUGH its exact mechanism of action remains unknown,[1] propranolol hydrochloride and related β-adrenergic blocking drugs have become some of the most important antihypertensive agents other than thiazide diuretics.[2,3] Propranolol is remarkably free of disturbing side effects,[4] and one authority in the United States now recommends that it be used in place of thiazides as "step 1" in the "step-care method" for treating hypertension[5] as it has been used in Europe. This trend is accentuated by the fact that diuretics commonly induce a variety of biochemical side effects,[6] including hypokalemia, hyperuricemia, and hyperglycemia, and most recently have been associated with increased levels of serum cholesterol and triglycerides.[7,8] Some authorities also believe that thiazides cause impotence and other subjective side effects.[9]

See also p 2004.

A Veterans Administration Cooperative Study comparing propranolol alone and in various combinations with other drugs to a standard regimen of hydrochlorothiazide and reserpine[10] indicated that, although not as effective as the standard regimen, propranolol alone controlled the BP in 52% of patients with mild to moderate hypertension, which approximates the magnitude of thiazide efficacy.

The present study was designed to compare propranolol and hydrochlorothiazide in a double-blind, controlled clinical trial to determine if one drug is superior to the other in terms of efficacy, adverse effects, or both. We also sought to determine the validity of the step-care algorithm in that it calls for the administration of diuretic as a step 1 drug to patients with hypertension.

SUBJECTS AND METHODS

This phase IV, double-blind, randomized, parallel study involved 906 patients in seven VA Medical Centers. Nonhospitalized male veterans aged 21 to 65 years with mild to moderate hypertension and

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an average untreated seated diastolic BP of 95 to 114 mm Hg composed the study population. Patients previously treated for hypertension underwent a two-week washout period before the placebo period.

Patients with known hypersensitivity to either propranolol, hydrochlorothiazide, or other sulfonamide derivatives were excluded. In addition, the presence of any one of the conditions listed in Table 1 excluded a patient.

Informed consent for each patient was obtained in accordance with US Department of Health, Education, and Welfare and VA guidelines. This study was approved by a central evaluation committee and human research committee as well as by similar committees in the participating medical centers. Safety criteria for discontinuing patient participation in the study are listed in Table 2.

After a single-blind placebo baseline observation period of four weeks, 683 patients whose diastolic BP were 95 to 114 mm Hg and who were compliant for two consecutive visits were randomized to one of the two double-blind regimens (propranolol or hydrochlorothiazide). This was followed by a ten-week dose-finding period, during which the clinic staff titrated the blinded drug upward until goal BP (90 mm Hg diastolic or less) was reached. Visits were scheduled every two weeks for the first four titration steps and at weekly intervals for the last two. Patients were withdrawn from the study if diastolic pressure on any visit was 120 mm Hg or greater.

Table 1.—Exclusion Criteria*

A mean untreated or post-washout diastolic pressure >114 mm Hg or <86 mm Hg
Hypertensive retinopathy (K-W scale) greater than grade II
History of hypertensive encephalopathy or stroke within six months
Serum creatinine level greater than 2.5 mg/dL
Myocardial infarction within six months or angina pectoris greater than New York Heart Association class II
Sinus bradycardia (<50 beats per minute) or heart block greater than first degree, or W-P-W syndrome
Atrial fibrillation
Frank congestive heart failure or left ventricular failure evidenced by at least two of the following: (1) recent dyspnea or orthopnea not of pulmonary origin; (2) ventricular diastolic gallop; (3) basal pulmonary rales; and (4) cardiothoracic ratio greater than 0.5
Patients with primary cardiac valve disease
Patients with Raynaud's disease or symptomatic and objective peripheral vascular disease
Bronchial asthma or chronic obstructive pulmonary disease
Allergic rhinitis during pollen season
Pulmonary hypertension or frank right ventricular failure due to primary or chronic pulmonary disease
Patients receiving adrenergic augmention psychotropic drugs including MAO inhibitors, amphetamine, and its derivatives
Collagen vascular diseases with the exception of rheumatoid arthritis
Pheochromocytoma, primary aldosteronism, or Cushing's syndrome
Malignancy, including leukemia and lymphoma
Diabetes mellitus if unstable, of preadult onset, or requiring pharmacologic treatment
History or evidence of psychiatrically documented nonsituational, clinically important mental depression
Patients regularly using transcendental meditation, biofeedback relaxation, or similar techniques
Patients with known gout
Severe alcohol abuse sufficient to interfere with compliance
Obesity: patients should be within 30% of expected weight/height relationship for applicable age
History of drug or narcotic abuse
Patients who have not given written informed consent
Chronic conjunctivitis or psoriasis

*K-W indicates Keith-Wagner scale; W-P-W, Wolff-Parkinson-White syndrome; MAO, monoamine oxidase.

The code name for the identical-appearing tablets containing either propranolol or hydrochlorothiazide was "propazide." The six strengths of both preparations were referred to as propazide B, C, D, E, F, and G. Propazide A was the placebo used during the prerandomization period. When propazide was propranolol, the doses B to G were 40, 80, 120, 160, 240, and 320 mg administered twice daily. When propazide was hydrochlorothiazide, doses B and C were 25 mg; D and E were 50 mg; and F and G were 100 mg administered twice daily. Although patients were generally advised to limit salt intake, there was no systematic control of their diet.

Patients were required to return their medication bottles at each visit. The remaining tablets were counted in another room, and patients were deemed to be compliant if they had consumed not less than 80% nor more than 110% of the prescribed number of tablets.

Trained observers, experienced in the use of a mercury sphygmomanometer, made all BP determinations. The fifth phase, or disappearance of the Korotkoff sounds, in the seated position was used as the index of diastolic pressure. History and physical examination were recorded, and the chest roentgenogram, ECG, and basic laboratory tests were performed during the placebo period. The experimental BP was defined as the average diastolic BP on the last two consecutive visits at the same dose level.

Laboratory evaluations included a complete blood cell count, urinalysis, and biochemical profile. These were performed on multichannel automated analyzers using the same methods for each hospital. Five of the centers determined baseline and stimulated plasma renin activity and 24-hour urinary excretion of sodium, potassium, and creatinine. The remaining centers performed modified glucose tolerance tests. These special tests will be the subject of separate communications.

This study was designed by a committee that included biostatisticians, some of whom participated in the analysis of these data and in the monitoring of the study. Paired and unpaired Student's t tests and χ^2 tests were used to assess statistically significant differences (defined as $P<.05$) between groups of data.

Patients who attained goal BP on two consecutive visits prior to titration to the maximum dose of propazide (level G) were "rapidly advanced" to visit 10. All patients reaching visit 10, whether by full titration or rapid advancement, were entered into a one-year chronic treatment phase if their diastolic BP was less than 100 mg Hg and if they were at least 6 mm Hg less than their original baseline value at randomization. A total of 394 patients (80.2% of 491 reaching visit 10) entered the chronic treatment phase and are the subject of a separate report. When there was less than one year remaining in the study, 119 new patients who reached the end of the dose-finding phase were terminated because of time limitations. A total of 610 patients completed the dose-finding phase.

When patients were terminated from the study, they were given a card of blister-packaged tablets that gradually tapered the propazide dose to zero in two weeks. Blister cards were marked and coded to begin at a dose one step below the level at the time of termination.

RESULTS

Comparability of Groups

Of the 906 patients entering this study, 683 (75.4%) met the requirements for randomization. The most

Table 2.—Criteria for Discontinuing Therapy*

Whenever the patient decides that it is in his best interest to be withdrawn from the study
Whenever the investigator deems it necessary or in the patient's best interest
Severe adverse effects
Development of myocardial infarction or development of or worsening of angina pectoris
Bradycardia <40 beats per minute in sitting position if symptomatic. If asymptomatic, continue medication and see in one week. If bradycardia <40 beats per minute persists, remove patient from the study
Development of bronchial asthma
Arrhythmias such as atrial fibrillation or flutter
Development of congestive heart failure. Inasmuch as this is one of the critical assessment events and in order that objective data be obtained, a patient will be considered to have congestive heart failure if two of the following four findings are present: (1) significant dyspnea defined as increasing exertional dyspnea, orthopnea and PND; (2) ankle edema—grade 2 or more out of a possible grade 4; (3) basilar rales or pleural effusion not due to pulmonary disease by x-ray film; (4) ventricular diastolic gallop (S-3).
New striate retinal hemorrhages in more than one quadrant, new cotton wool exudates or papilledema in optic fundi associated with hypertension and not with diabetes or other disease. This finding is to be confirmed by a second observer, preferably an ophthalmologist
Cerebral hemorrhage, subarachnoid hemorrhage, or cerebral thrombosis
Dissecting hematoma of the aorta
Acute hypertensive encephalopathy
Thrombocytopenic purpura or agranulocytosis
Greater than first-degree AV block
Pulmonary embolism or infarction
Psychiatrically confirmed depressive state
Serum creatinine level greater than 2.5 mg/dL and 50% higher than baseline
Development of symptomatic and objective peripheral vascular insufficiency or Raynaud's phenomenon
Development of rash, confirmed by dermatologist and considered to be drug induced
Development of eye complaints with objective slit-lamp findings by ophthalmologist or objective findings on eye examination that the ophthalmologist cannot explain on the basis of a routine ophthalmologic diagnosis and that he feels in any way could be related to the drug therapy
Patient failing to meet two consecutive clinic appointments without a legitimate excuse or interruption of therapy for more than 21 days
Patient failing to take at least 80% of the study medication on three consecutive visits during the chronic treatment phase
Seated diastolic BP >119 mm Hg on any visit
Severe, symptomatic hypotension with diastolic BP >90 mm Hg and on the lowest dose of propazide†

*PND indicates paroxysmal nocturnal dyspnea; AV, atrioventricular.

†"Propazide" was the code name for identical-appearing tablets containing either propranolol hydrochloride or hydrochlorothiazide.

common causes for prerandomization dropout were noncompliance (uncooperative or unreliable, 26%; pill count violations, 16%) and BP above or below the randomization criteria (26%). The 683 patients were randomized equally (340 to propranolol, 343 to hydrochlorothiazide), and the groups were statistically alike in regard to age, weight, race, and prior treatment (Table 3), heart rate and BP (Table 4), and baseline laboratory data (Table 5). By design, randomization within each clinic was also equal, but some clinics had a higher percentage of blacks than others.

BP and Heart Rate Changes

Table 4 displays the effects of propranolol and hydrochlorothiazide on BP and heart rate. Propranolol was associated with a lowering of the heart rate by 16 beats per minute, whereas hydrochlorothiazide administration resulted in an increase of 2.7 beats per minute.

Both drugs effectively lowered both systolic and diastolic BP; hydrochlorothiazide was significantly more effective for systolic ($P<.001$), but of borderline significance as more effective for diastolic ($P=.03$). Hydrochlorothiazide excelled over propranolol significantly ($P<.001$) in lowering systolic BP in the total group because of its greater efficacy in black patients. Although hydrochlorothiazide was associated with a reduction of systolic pressure 2.1 mm Hg more than propranolol in white patients, the difference was not significant. Hydrochlorothiazide was also more effective in reducing diastolic pressure in the total group even though propranolol was more effective by 1.7 mm Hg ($P=.02$) in the white patients.

There was no significant difference in the number of patients who achieved goal BP (propranolol, 57.0%; hydrochlorothiazide, 64.1%). This seemed, however, to result from a balance of opposing effects. Propranolol was somewhat more effective in whites (propranolol, 61.7%; hydrochlorothiazide, 55.3%), but the difference did not achieve statistical significance; however, hydrochlorothiazide was substantially more effective in blacks (71.3% *v* 53.5%; $P=.001$).

Although there was no predetermined systolic pressure defined as a goal in this protocol, we examined the percentage of patients with systolic pressure equal to or less than 140 mm Hg as another measure of drug efficacy. Hydrochlorothiazide was significantly more effective (84.9% *v* 65.8%; $P<.001$) in the total group, in black patients (87.7% *v* 64.1%; $P<.001$), and in the white patients (81.6% *v* 68.0%; $P=.015$). In contrast to these between drug differences, there were no significant racial differences in systolic pressure goal effect within each drug group. Propranolol was associated with a systolic BP reduction to or less than 140 mm Hg in 64.1% of black patients and 68.0% of whites, compared with 87.7% black and 81.6% white associated with hydrochlorothiazide.

Table 6 displays four negative aspects of treatment with the two drugs. The percent of patients remaining at or above 160 mm Hg systolic or 100 mm Hg diastolic can be taken as a measure of drug failure. There were significantly fewer systolic failures for hydrochlorothiazide, with the greatest difference being a 9.4% failure rate for whites taking propranolol compared with 1.4% for whites taking hydrochlorothiazide ($P<.001$). There were significantly more diastolic failures in black patients compared with white patients taking propranolol (17.6% *v* 8.6%; $P=.04$), but not in those taking hydrochlorothiazide (7.6% *v* 10.6%).

One concern relevant to any treatment mode is whether a substantial number of patients have an effect opposite to that intended. Table 6 displays the percentages of patients who had an actual increase of 1 or more mm Hg in systolic or diastolic pressure. Nearly one fifth of the

Table 3.—Baseline Demographic Data and Prior Treatment Status*

	Propranolol Hydrochloride	Hydrochlorothiazide
N	340	343
Age, yr	49.6 ± 9.8	49.8 ± 9.9
Weight, kg	86.6 ± 15.0	85.7 ± 14.1
% Black	37.7	36.9
Prior treatment status, %		
No prior prescription	36.6	39.1
Diuretic alone	17.9	18.7
Nondiuretic alone	6.2	3.2
Diuretic plus nondiuretic	36.2	35.8
Unknown medication	2.1	3.5

*Age and weight are expressed as mean ± SD. None of these differences is statistically significant.

Table 4.—Baseline Data and Effect of Treatment on Heart Rate and BP*

		Propranolol Hydrochloride	Hydrochlorothiazide	P Value†
Heart rate, bpm	B	76.9 ± 10.4	76.7 ± 11.5	NS
	E	60.9 ± 10.0	79.4 ± 11.6	<.001
Systolic BP, mm Hg	B	146.0 ± 14.4	146.6 ± 15.6	NS
	E	134.8 ± 16.3	128.8 ± 12.2	<.001
Diastolic BP, mm Hg	B	101.6 ± 4.6	101.3 ± 4.5	NS
	E	90.5 ± 7.6	89.4 ± 6.5	.04
Δ Systolic BP, mm Hg		−10.4 ± 12.8	−16.1 ± 13.6	<.001
W		−13.2 ± 13.1	−15.3 ± 12.0	NS
B		−8.2 ± 12.2	−20.3 ± 14.3	<.001
Δ Diastolic BP, mm Hg		−10.8 ± 7.0	−12.0 ± 6.5	.03
W		−12.6 ± 6.6	−10.9 ± 5.7	.02
B		−9.5 ± 7.0	−13.0 ± 7.0	<.001
% reaching goal		57.0	64.1	NS
% whites at goal		61.7	55.3	NS
% blacks at goal		53.3	71.3	<.001
% ≤ 140 mm Hg systolic‡		65.8	84.9	<.001
% white ≤ 140 mm Hg systolic‡		68.0	81.8	.015
% black ≤ 140 mm Hg systolic‡		64.1	87.7	<.001

*Numbers are mean ± SD. B indicates baseline; E, treatment end point; Δ BP=E-B; goal=BP <90 mm Hg diastolic; bpm, beats per minute.

†Comparison of propranolol *v* hydrochlorothiazide.

‡Based on treatment endpoint pressures.

patients receiving propranolol increased their systolic pressure, with the bulk of these among blacks (24.1%) but still twice the number of failures in whites for propranolol as for hydrochlorothiazide. There were far fewer patients who increased their diastolic pressure; however, there were significantly more such failures in blacks taking propranolol than whites (10.0% *v* 3.1%; $P=.04$). If only the patients who had an increase of more than 10 mm Hg systolic are counted, then 6.4% of the total propranolol and 0.3% of the total hydrochlorothiazide population would be included. For white patients, 4.7% receiving propranolol *v* 0.7% receiving hydrochlorothiazide had systolic pressure increases of more than 10 mm Hg. The respective values for black patients are 7.6% and 0.0%. Only three patients experienced a systolic BP increase in excess of 20 mm Hg. All were taking propranolol; two were black.

The magnitude of diastolic pressure increase was smaller. Six patients (five black) taking propranolol had a diastolic pressure increase of more than 5 mm Hg *v* two black patients taking hydrochlorothiazide.

The Figure displays the drug dose required to achieve goal BP in all of the patients where diastolic BP was reduced to less than 90 mm Hg on two consecutive visits. The first titration step of hydrochlorothiazide (25 mg twice daily) controlled 52.0% of the patients who achieved goal BP, compared with 14.9% of the patients treated with propranolol hydrochloride who achieved control at the first level (40 mg twice daily). The second level (50 mg twice daily) of hydrochlorothiazide controlled an additional 29.0% (81% for both doses combined), while propranolol hydrochloride had to be titrated to the fourth step (160 mg twice daily) to control a total of 80.2% of responders. It is interesting that change of hydrochlorothiazide to levels C, E, and G, which effected no actual change in drug dose, were nevertheless associated with an increase of 18.5%, 10.0%, and 9.5% responders, respectively.

Terminations

A total of 73 (10.7%) of the patients were dropped from the study after randomization. Of these, 42 (57.5%) were in the propranolol group and 31 were taking hydrochlorothiazide. The difference was not significant. Terminations were classified as either medical (adverse reactions, BP out of control, intolerable symptoms, or serious abnormal laboratory results) or administrative (interruptions in treatment for more than 21 days, uncooperative or unreliable in keeping appointments, unrelated intercurrent illness, or withdrawal of consent). Each termination was reviewed by several different observers to try to determine that an administrative termination was not more likely owing to a medical reason (eg, a patient refusing to return because he was having apparently intolerable symptoms caused by propazide). Medical terminations occurred in 13 (3.8%) of the patients receiving propranolol and six (1.7%) of the patients receiving hydrochlorothiazide ($\chi^2=2.0036$; $P=.157$). Terminations related to propranolol were due to diastolic BP greater than 119 mm Hg in four, intolerable symptoms such as lethargy, dreams, depression, dizziness, nausea, blurred vision, and headache in four, elevated blood glucose levels in two, and one each of skin rash, bronchospasm, and congestive heart failure with wheezing. Terminations related to hydrochlorothiazide were due to diastolic BP higher than 119 mm Hg in two, intolerable symptoms such as diuresis, weakness, dyspnea, chest tightness, headache, and fatigue in two, and abnormal laboratory data in two. One of the latter was a compulsive water and beer drinker who had a history of hyponatremia. A "flulike" syndrome

Table 5.—Serum Concentration of Selected Substances at Baseline and at the End of Drug Titration*

Test		Propranolol Hydrochloride					Hydrochlorothiazide					
		All	P†	W	B	P‡	All	P†	W	B	P‡	P§
Urea nitrogen, mg/dL	B	13.7±3.7	...	14.5±4.1	13.2±3.3	.001	14.0±3.9	...	15.2±3.8	13.0±3.6	<.001	NS
	E	14.8±3.8	...	15.9±3.4	13.9±3.4	<.001	16.7±4.6	...	17.3±4.5	16.2±4.6	NS	<.001
	E−B	1.1±3.1	<.001	1.5±3.3	0.7±2.9	.05	2.8±4.4	<.001	2.0±4.0	3.4±4.6	.009	<.001
Creatinine, mg/dL	B	1.2±0.2	...	1.2±0.2	1.2±0.2	NS	1.2±0.2	...	1.1±0.2	1.2±0.2	NS	NS
	E	1.2±0.2	...	1.2±0.2	1.2±0.2	NS	1.2±0.2	...	1.2±0.2	1.3±0.3	.002	NS
	E−B	.04±0.2	.003	.03±0.2	.04±0.2	NS	.07±0.3	<.001	.02±0.2	.11±0.3	.006	NS
Potassium, mEq/L	B	4.2±0.4	...	4.27±0.4	4.17±0.4	.02	4.2±0.7	...	4.36±0.9	4.17±0.4	.01	NS
	E	4.4±0.4	...	4.51±0.4	4.31±0.3	<.001	3.6±0.5	...	3.49±0.6	3.66±0.5	.006	<.001
	E−B	.18±0.4	<.001	.24±0.4	.13±0.4	.04	−.67±0.9	<.001	−.88±1.1	−.50±0.6	<.001	<.001
Glucose, mg/dL	B	100±23	...	103±23	96±23	NS	100±25	...	105±29	97±21	.002	NS
	E	102±20	...	107±20	96±20	<.001	108±23	...	110±21	102±24	.003	NS
	E−B	4.0±17	<.001	5±16	3±18	NS	4.0±23	.004	4±26	4±17	NS	NS
Uric acid, mg/dL	B	6.4±1.3	...	6.52±1.3	6.33±1.4	NS	6.0±1.4	...	6.57±1.3	6.50±1.6	NS	NS
	E	6.6±1.3	...	6.66±1.2	6.58±1.3	NS	8.0±1.7	...	7.94±1.6	8.14±1.8	NS	<.001
	E−B	.21±1.0	NS	.19±0.9	.22±1.0	NS	1.47±1.4	<.001	1.35±1.6	1.58±1.3	NS	<.001
Calcium, mg/dL	B	9.5±0.5	...	9.44±0.5	9.50±0.5	NS	9.3±0.9	...	9.34±0.7	9.37±1.0	NS	NS
	E	9.4±0.4	...	9.31±0.5	9.48±0.4	.007	9.6±0.4	...	9.60±0.4	9.71±0.4	.05	<.001
	E−B	−.05±0.5	NS	−.12±0.5	−.01±0.5	NS	.31±0.9	<.001	.28±0.8	.34±1.0	NS	<.001
Cholesterol, mg/dL	B	221±47	...	220±48	222±47	NS	224±47	...	226±49	223±45	NS	NS
	E	217±46	...	221±48	214±43	NS	231±48	...	234±51	229±46	NS	<.001
	E−B	−5.2±33	.01	1±35	−8±31	NS	8.8±39	<.001	7±44	10±34	NS	<.001
Triglycerides, mg/dL	B	166±140	...	206±177	135±95	<.001	184±198	...	222±210	154±183	.002	NS
	E	191±150	...	234±189	159±101	<.001	220±275	...	276±350	172±177	.002	NS
	E−B	27±131	<.001	31±173	27±88	NS	34±266	NS	56±325	14±251	NS	NS

*Values are given as mean ± SD; B indicates baseline; E, experimental.
†*P* value for difference between E and B for all patients in that treatment group.
‡*P* value for the differences in E, B, and E-B between white and black patients in that treatment group.
§*P* value for the differences in B, E, and E-B between propranolol and hydrochlorothiazide treatment group.

Table 6.—Selected Negative Parameters of BP Effect of Both Drugs*

Drug Patients	All Patients			Propranolol Hydrochloride			Hydrochlorothiazide		
	Propranolol Hydrochloride	Hydrochlorothiazide	P	W	B	P	W	B	P
% DBP ≥ 100	13.8	9.0	NS	8.6	17.6†	.04	10.6	7.6†	NS
% SBP ≥ 160	8.1	1.6	<.001	9.4†	7.1†	NS	1.4	1.8†	NS
% SBP↑	19.8	7.1	<.001	14.1	24.1†	.04	7.1	7.0†	NS
% DBP↑	7.0	5.1	NS	3.1	10.0	.04	5.7	4.7	NS

*P values are for the significance of the difference between the pair to the left. NS = P > .05. DBP indicates diastolic BP; SBP, systolic BP.
†Indicates a significant difference between the effect of the two drugs in the same race.

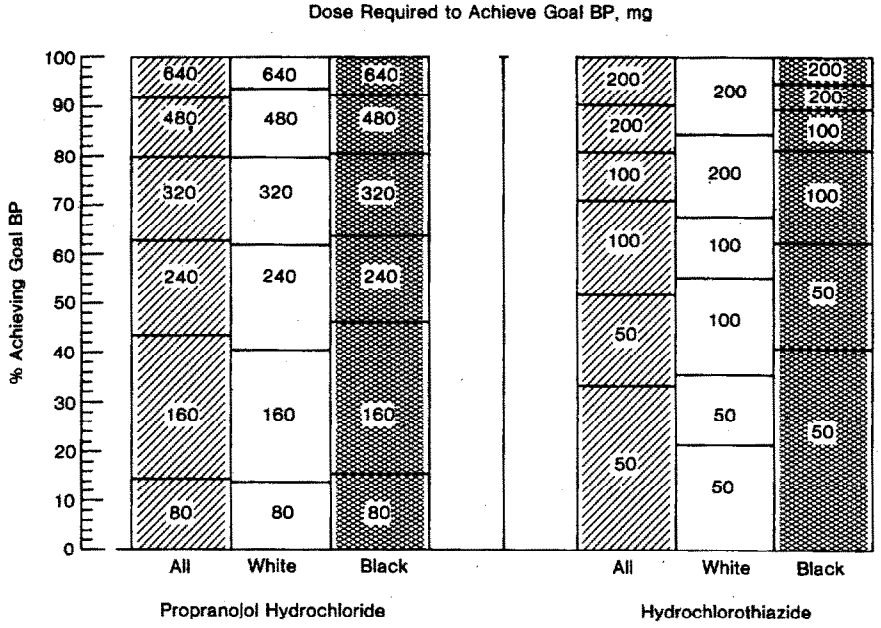
developed, and he was discovered to have a serum sodium level of 108 mEq/L. Propazide administration was discontinued. He responded to treatment with normal saline and was discharged feeling well. He was subsequently rechallenged with hydrochlorothiazide, had successful reduction of his BP, and remained normonatremic. Seven white and six black patients taking propranolol were withdrawn for medical reasons, compared with five white and one black patient taking hydrochlorothiazide.

Patient complaints will be discussed in detail in a separate report. In essence, this study indicated that there were no unexpected complaints. Symptoms related to the CNS were significantly more frequent in patients taking propranolol. Diarrhea was more common with propranolol, and constipation was associated with hydrochlorothiazide. Both drugs were associated with a low level of sexual dysfunction, but significantly more occurred in the patients taking hydrochlorothiazide; they also had more complaints of decreased libido. Selected laboratory values are displayed in Table 5.

COMMENT

These data demonstrate that in the short-term titration period studied, hydrochlorothiazide was generally more efficacious than propranolol in lowering BP. An important part of this effect was racial, with blacks being more likely to respond to hydrochlorothiazide than to propranolol. On the other hand, there was not much difference in response to the two drugs in the white patients. The differences that were demonstrated were in favor of hydrochlorothiazide for systolic pressure and propranolol for diastolic pressure. The diastolic pressure difference may have been caused by the lower heart rate, in that more time was permitted for diastolic runoff.

The observations on those patients who had an actual increase in BP suggest a potential risk, especially for black patients treated with proprano-



Distribution of drug dose required to achieve goal BP (<90 mm Hg). Only patients who actually achieved goal BP are included. Numbers in bars indicate drug dose in milligrams. For hydrochlorothiazide, lower of two identical numbers indicates first titration step, and higher indicates second, or "dummy," titration step. "All" represents black and white groups combined. There was no racial effect in dose for propranolol hydrochloride, but there was superior response (P=.004) for black patients taking hydrochlorothiazide.

lol monotherapy. The risk was also present for white patients, but to a lesser extent.

One of the main reasons for initiating this study was the question of whether or not it was appropriate to begin the drug treatment of hypertension with a diuretic routinely, as had been proposed by the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure,[11] or to begin with a β-blocker. This empirical approach is at odds with the more elaborate volume-vasoconstriction scheme of Laragh,[5] who recommended that drug therapy be selected on the basis of renin profiling. If profiling could not be done, he suggested that propranolol should be used as the step-one drug and diuretic added only if it failed. If the two drugs lowered BP, propranolol could be withdrawn to determine whether the BP would be controlled with diuretic alone. Obviously, this schema is more complicated and requires more patient visits than the less individualized step-care system. The data presented herein seem to support the general use of diuretic as a first-line drug, especially for black patients. Even in the white population, diuretic seemed to have little if any disadvantage with respect to propranolol.

Major studies on hypertension in the United States have included a large black population that is disproportionate even to the fraction of blacks in the United States. Studies from Europe and the United Kingdom tend to include few or no blacks, so that the established habits on each side of the Atlantic would tend to be reinforced by their selection of patients.

Several other studies have suggested that blacks are less responsive to β-adrenergic blocking agents than are whites.[12-16] Abson et al[15] could induce significant BP reduction in Zimbabwean blacks only with a high dose (200 mg) of atenolol. The results were also less favorable than in a prior study of white patients.[17] Seedat[14] compared atenolol (100 mg) with chlorthalidone (25 mg) in 24 Zulus. Chlorthalidone produced a small effect and atenolol no effect, but the combination was effective. He concluded that "beta-blockers should not be regarded as baseline treatment of hypertension in blacks."[14]

The mechanisms for the observed differences in drug response are not known. Examination of the preliminary data on 24-hour sodium and potassium excretion shows that there was no racial difference in sodium excretion (and, therefore, consumption), but that blacks excreted only about 60% of the quantity of potassium excreted by whites. Possibly this may be a reflection of a lower dietary intake of potassium-rich fresh fruits, vegetables, and lean meats by blacks, but data are lacking to support this point. The electrolyte excretion data will be presented separately. There is some evidence to suggest that a reduced potassium intake in comparison with sodium may contribute to hypertension. For example, potassium is said to have a natriuretic effect.[18] Watson et al[19] studied pooled cross-section data from 662 black and white females in regard to systolic BP and urinary electrolyte excretion. They found the urinary sodium/potassium ratio to be directly related to systolic BP and suggested a moderating role for potassium. Luft et al[20] conducted a detailed study of 347 normotensive black and white men and women. The urine sodium/potassium excretion ratio was higher in blacks by about 50%, and blacks were less efficient than whites in handling an acute sodium load.

Many workers have explored the reasons for the observed racial differences in hypertension. Gillum[21] has carefully reviewed data in regard to differences in genetic factors and personal characteristics including skin color, renal physiology, endocrine factors, autonomic nervous system function, cardiac function, and environmental factors. He pointed out the difficulties of separating specific factors from numerous confounding variables.

Plasma volume is more likely to be expanded in blacks than in whites, and plasma renin activity tends to be lower.[22] Mitas et al[23] studied blood volume and plasma renin activity (PRA) in 29 normotensive persons, including 14 blacks, and 36 hypertensive persons, nine of whom were black. They found differences in volume and PRA between blacks and whites that they believed to reflect basic racial differences. On the other hand, Messerli et al[24] studied 126 black and white patients with essential hypertension and found that, when matched for age or level of

arterial BP, systemic hemodynamics were similar. They concluded that the basic pathophysiology of hypertension was not different in black patients with essential hypertension. Holland et al[25] used three methods—intravenous furosemide test, ambulation during placebo treatment, and ambulation during spironolactone and hydrochlorothiazide treatment—to determine renin status in 26 black hypertensive women. In only seven did the three methods coincide. They concluded that "since black women with both low and normal renin activity are quite responsive to diuretics, renin classification to guide initial antihypertensive selection is not warranted."[25] Plasma renin data from our study will be presented separately.

A curious absence of hypertension seems to occur in blacks with sickle cell disease.[26] This may be due to the salt-wasting nephropathy of sickle cell disease.

Other possibly important racial differences include difference in the ouabain-resistant pathway of RBC cation transport.[27] The difference in response to drugs does not appear to be related to differences in aldosterone excretion[28] or plasma norepinephrine concentration.[29,30] It is possible that blacks have some deficiency in the kallikrein-kinin natriuretic vasodilator system[31]; however, the observed differences might be due to other factors such as dietary sodium and potassium intake. White hypertensive persons have greater dopamine-β-hydroxylase activity than blacks.[32]

This study confirmed the relative ease of titration with hydrochlorothiazide in that 80% of the patients responded by the second titration step, whereas four titration steps above the initial dose with propranolol were required to reach the same goal. In practice, however, many physicians might not include the 240-mg level and, thereby, would reduce the number of steps to three. Also, it is likely that patients who did not respond to 320 mg of propranolol or 100 mg of hydrochlorothiazide would have a "step-2" drug added rather than continue the titration upward. In the total group, an average of 268 mg of propranolol and 93 mg of hydrochlorothiazide was required to achieve control. White patients required an average of 269 mg of propranolol hydrochloride, blacks 267 mg. White patients required 114 mg of hydrochlorothiazide, blacks 79 mg (P=.004). Thirty-eight patients (19.0%) who failed to achieve goal BP while taking 100 mg of hydrochlorothiazide did achieve goal when they received 200 mg. This suggests that 100 mg is not necessarily maximal.

Our observation of continued response to hydrochlorothiazide on the same dose after a dummy titration step suggests that it is important to provide enough time for a response to hydrochlorothiazide before titrating upward. Interim visits no doubt serve to reinforce salt restriction, compliance, and a sense of confidence in the therapist, which are independent of drug effect per se. Patients who are nearing goal BP ought to be given more time to respond rather than being titrated upward at once or having another drug added.

Considerable attention has been paid to the metabolic adverse effects of both propranolol and hydrochlorothiazide. Most studies that have looked at these laboratory changes have been cross-sectional studies of changes induced by relatively acute pharmacologic manipulation. This study falls into that category. We indeed did demonstrate statistically significant increases in serum urea nitrogen, uric acid, calcium, and cholesterol levels with hydrochlorothiazide acutely as compared with propranolol over the short term. We also observed a statistically significant decrement in the serum potassium level with hydrochlorothiazide, whereas the potassium level tended to increase with propranolol. The biological significance of these changes has not been fully elucidated.

The issue of hypokalemia perhaps has been the one most vigorously debated. If the work of Holland and co-workers[33] showing an increase in ventricular ectopic activity associated with hypokalemia is confirmed, then it would seem to be necessary to pay considerably more attention to even trivial decrements in serum potassium. Indeed, Caralis et al[34] have evidence that diuretics do increase ventricular ectopic activity, but only in a susceptible patient population consisting of elderly patients with identifiable, preexisting organic heart disease.

The present data suggest that many of the responders to hydrochlorothiazide achieved their benefit at low doses of the drug. Use of these lower doses of diuretic should cause less perturbation of serum potassium levels.[35] It is also possible that these short- or intermediate-term cross-sectional studies are not providing a representative picture of long-term maintenance therapy. Berglund and Andersson[36] demonstrated that in a group of patients followed for six years there were no material differences between the metabolic adverse effects of propranolol and hydrochlorothiazide. If this is true for the long term, then it is possible that there might be undue concern over the short-term changes.

If the observations from an acute study of the effects of ethanol consumption on propranolol clearance[37] can be extrapolated to habitual alcohol abusers, then an additional potential disadvantage of propranolol might be identified. Ethanol ingestion increases metabolic clearance of propranolol and decreases its antihypertensive effect. The extent to which this might have diminished the efficacy of propranolol compared with hydrochlorothiazide in our study is not known.

Cost of drugs is a factor that may be easily forgotten. In a federal hospital the cost of 50 mg of hydrochlorothiazide twice daily for 30 days is 60 cents, whereas the cost of 160 mg of propranolol hydrochloride twice daily for 30 days is $14.40 in 1982 dollars. The actual cost to the patient in a community pharmacy will vary, but is usually much higher.

CONCLUSION

This short-term trial of drug monotherapy for patients with mild to moderate hypertension demonstrated that hydrochlorothiazide was at least as effective as propranolol for white patients and was superior to propranolol in blacks. Furthermore, hydrochlorothiazide proved less likely to elevate BP in those patients who did not respond to treatment and required fewer titration steps to achieve control than propranolol. Nevertheless, what is good for groups of patients does not necessarily obtain for a given individual. Therapeutic decisions must continue to rest

on specific indications, contraindications, simplicity of titration, patient acceptance, potential undesirable effects, and cost.

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